ABSTRACT

Noninvasive procedures targeting the elimination of unwanted adipose tissues have recently been developed. Injection adipolysis is the term for the injection of cytotoxic substances into these tissues, with the intent of cosmetic improvement by volume reduction. Initial attempts in the field utilized intravenous preparations of sodium deoxycholate and soy-derived phosphatidylcholine, approved for the intravenous treatment of fat emboli and dyslipidemias in countries outside the United States. It was initially purported that the active ingredient in these injections was phosphatidylcholine. Subsequent research discovered that injections of sodium deoxycholate alone were capable of inducing cellular lysis *in vitro*. These compounds also demonstrated an affinity for adipose tissue, sparing the overlying dermis and epidermis. The United States Food and Drug Administration (FDA) recently approved a formulation of sodium deoxycholate 10mg/mL for subcutaneous injection with the indication of aesthetic improvement of excess submental fat. It has shown moderate efficacy with appropriate patient selection and good patient satisfaction. However, previous research leading to the development of this drug proposed that including phosphatidylcholine

[Abstract continued on next page]

REVIEW

Injection Adipolysis: Mechanisms, Agents, and Future Directions

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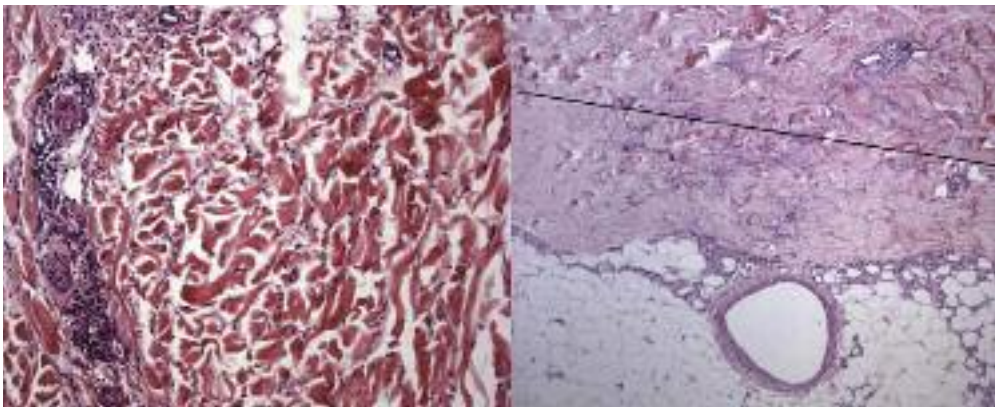

TUMESCENT LIPOSUCTION WAS developed by dermatologist Jeffrey Klein in 1987 and has since become the gold standard among techniques for subcutaneous adipose tissue removal.[1] Numerous noninvasive and lipolytic alternatives to liposuction have been developed since that time, including radiofrequency, high intensity focused ultrasound (HIFU), cryolipolysis, and nonthermal ultrasound.[1,2]

Among the newest modalities for the treatment of unwanted subcutaneous fat deposits is injection adipolysis, which utilizes products containing the active ingredient sodium deoxycholate (SDC). This technique has sparked interest due to limited downtime and ease of subcutaneous injection, and confers the ability to target small pockets of adipose tissue not amenable to treatment with other modalities.[2]

The practice of mesotherapy, coined by French physician Michel Pistor in the 1950s, refers to subcutaneous injection of substances designed to improve the appearance of adipose tissues.[3] Maggiori was the first to describe the use of mesotherapy preparations containing phosphatidylcholine (PC) dissolved in SDC.[4] Soon thereafter, numerous pilot studies reported reduction of adipose tissues with these injections.

The most well-known of these early agents was Lipostabil Endovena® (Aventis Pharma, Germany), an intravenous agent for the treatment of hyperlipidemia, fat emboli, diabetic angiopathy, atherosclerosis, and other intravascular lipid abnormalities.[5–9]

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[Abstract continued]

to a more appealing cosmetic result, with decreased severity of injection-site reactions. Future drugs in the field of injection adipolysis may attempt to combine these ingredients for improved cosmesis and tolerability.

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Small studies had previously reported positive effects of this IV agent on systemic lipid profiles, prompting study as a mesotherapeutic agent.[10,11]

Despite rampant use in Brazil, with thousands of patients seeking injections for cellulite, back rolls, and lower eyelid fat pad herniation, Lipostabil was banned in December 2002 for cosmetic use by ANVISA, the Brazilian equivalent of the FDA, as there were no clinical trials supporting efficacy or safety of the drug.[12,13] The Medicines and Healthcare Products Regulatory Agency in the United Kingdom and the FDA subsequently issued strong warnings against their use.

Further research elucidated SDC as the active ingredient in these mesotherapeutic solutions, culminating in the FDA's approval of ATX-101, marketed as Kybella® (Kythera Biopharmaceuticals, subsidiary of Allergan, Westlake Village, California). This preparation of sodium deoxycholate 10mg/mL was approved for the aesthetic improvement of "moderate-to-severe convexity or fullness associated with submental fat in adults," and is the first FDA-approved drug for injection adipolysis.[14]

MECHANISM OF ACTION AND HISTOLOGY

Effects of subcutaneous injection of solutions containing PC and SDC were initially debated, and it was proposed that they induced breakdown of stored triglycerides within adipocytes and activated intracellular lipases. This theory, based upon PC's effect on systemic triglyceride levels, and its ability to emulsify fats for transport, led to the hypothesis that PC was the active ingredient.[10,12,15]

Subsequent research by Rotunda et al[5] in 2004 revealed that SDC was likely the active ingredient, acting as a biologic detergent and disrupting cell viability. Laboratory experiments revealed a dose-dependent cellular lysis in cultured cells exposed to SDC.[4,5,7,16,17]

Researchers proposed that SDC acted as a detergent, resulting in compromise of the cell's phospholipid bilayer and leading to cellular lysis. The solubilization of phospholipid bilayers into mixed micelles by detergents was first described by Lichtenberg in 1983.[18] Ionic detergents, such as SDC, disrupt the integrity of membranes by introducing their polar hydroxyl groups into the hydrophobic core of the bilayer. Eventually, solubilization of membrane-associated proteins occurs, and the cell membrane collapses into mixed micelles of phospholipids and detergent molecules.[19]

Experiments utilizing cell culture, metabolic assays, and histological assessment have independently verified this hypothesis, by testing isolated SDC compounds, which were capable of inducing cellular lysis, and resultant necrosis, in various tissue types.[3,7,16] Most cells were destroyed within 15 minutes of incubation with solutions *in vitro* (Table 1).[7]

These experiments also revealed that mature adipocytes were more resistant to detergent-induced cellular lysis than other cell types *in vitro*, raising the question of how safe these agents would be, should injection accidentally occur outside a fat compartment.[7] Follow-up studies revealed that due to SDC's affinity for albumin, the low concentration of albumin and other proteins surrounding adipose tissues might account for their relative susceptibility to these compounds (Table 2). Mouse tails injected with SDC

TABLE 1. Time required to induce >90 percent observable cell death as confirmed by acridine orange staining in cellular populations exposed to compounds containing phosphatidylcholine dissolved in sodium deoxycholate[7]

TIME TO 90 PERCENT CELL DEATH	CELL TYPE
90 seconds	Preadipocytes
Six minutes	Vascular smooth muscle cells, skeletal myotubes, renal epithelial cells
15 minutes	Immature adipocytes

TABLE 2. Concentration of SDC required to induce lysis of cultured adipocytes *in vitro*

ALBUMIN CONCENTRATION	LD_{50}
None	0.045%
0.7%	0.075%
1.3%	0.100%

Increasing concentrations of albumin increased the observed LD_{50} in a dose-dependent manner.[20]

revealed near complete sparing of muscle layers, dermis, and epidermis on histologic examination, despite remarkable necrosis and fibrosis of subcutaneous adipose tissue.[20]

Testing isolated solutions of PC was initially deemed impossible, as it is insoluble in aqueous solution. In 2009 however, Duncan et al[17] utilized inert mineral oil as a solvent, showing that PC alone was incapable of causing the cellular lysis seen with total PC/SDC solutions.

Use of PC in mixed solutions was observed to provide a pH buffer, and histology was markedly different in patients treated with mixed solutions when compared to SDC alone. Specimens demonstrated dispersed fibrotic and necrolytic effects of SDC, as opposed to focal areas of fat necrosis.[17] Serial histologic examination supported these findings, with marked and immediate fat necrosis with injection of SDC alone, whereas mixed solutions showed minimal change soon after injection. Areas injected one week prior to microscopic examination revealed small areas of fat necrosis within the tissue exposed to PC/SDC solution, as well as intense inflammation and fibrosis in areas treated with isolated solutions of SDC. At two-weeks post-injection, histology specimens displayed large moth-eaten areas of fat necrosis in the SDC alone patients, and more organized fat necrosis from mixed PC/SDC solutions; the latter demonstrating inflammation, neovascularization, fat cell lysis, and macrophage infiltration. At one month after injection, a severely fibrotic appearance was seen in subcutaneous tissue treated with SDC alone, whereas combined solutions demonstrated a "fractionated response", with smaller areas of fat necrosis separated by islands of normal-appearing adipose. Treatment areas exhibit a sterile cellulitis with neutrophil-rich infiltrates in the deep reticular dermis present in all patients (Figures 1 and 2).[17]

Radiolabeled studies have shown injected SDC enters GI circulation within a few days of injection, undergoing fecal elimination similarly to endogenous bile acids. Some theorize that PC may assist in emulsification of debris formed after adipolysis, assisting in lymphatic drainage. This theory remains untested, and radiolabelled studies assessing the fate of this lipid-rich cellular debris may assist in further delineating post-injection tissue effects and further differences with solutions containing the mixture of both ingredients.[8,17,20]

CLINICAL TRIALS

Many studies of mesotherapy solutions containing PC/SDC utilized compounded formulations similar to Lipostabil, and were not FDA approved. Various injection sites were tried in these pilot studies, including lower lid fat pad herniation, large volume injection of "cellulite" in the gluteotrocanteric region, "back rolls," and lipomas.[9,17,21–24]

ATX-101 showed promising results in the first FDA-approved clinical trials of an SDC-based solution. The results of a multicenter study of 363 patients who expressed dissatisfaction with their submental area was reported in 2014. Patients were randomized to receive either drug or placebo for 1 to 4 treatment sessions.

Out of 241 patients in the drug arm, 19 discontinued treatment early due to adverse effects. One of 122

patients in the control arm discontinued treatment. Significant improvement was reported by 59.2 percent of patients in the lower dose group, 65.3 percent in the higher dose group, and 23 percent of patients in the placebo group.[25]

The REFINE-1 study, published in January 2016, is the largest trial to date, with 506 total subjects. In addition to visual scores, this study utilized magnetic resonance imaging (MRI) evaluation of the preplatysmal fat pad in 224 patients. The authors determined that 46.3 percent of participants demonstrated radiographic response in the treatment group, compared with 5.3 percent of the placebo group.[26]

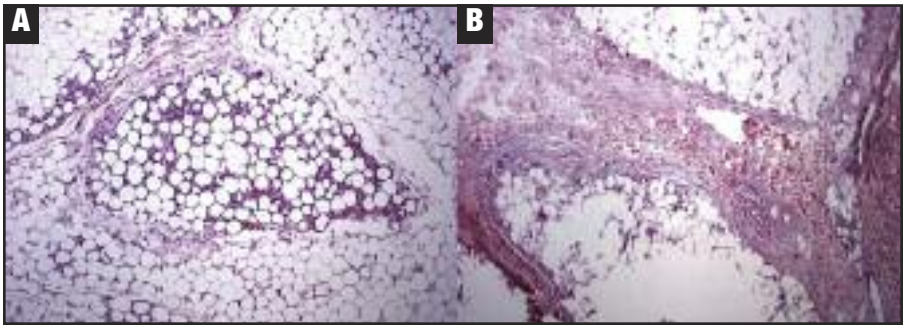

Figure 1. (A) Panniculitis induced by mixed injection of SDC/PC solution 3 weeks prior; evenly distributed lobular pattern of fibrosis; (B) Adipose injected with 4.2% deoxycholate 4 weeks after SDC injection, exhibiting pronounced septal fibrosing panniculitis. Figure adapted from Duncan D, Rubin JP, Golitz L, et al. Refinement of technique in injection lipolysis based on scientific studies and clinical evaluation. *Clin Plast Surg.* 2009;36(2):195–209. Elsevier. Adapted with permission.

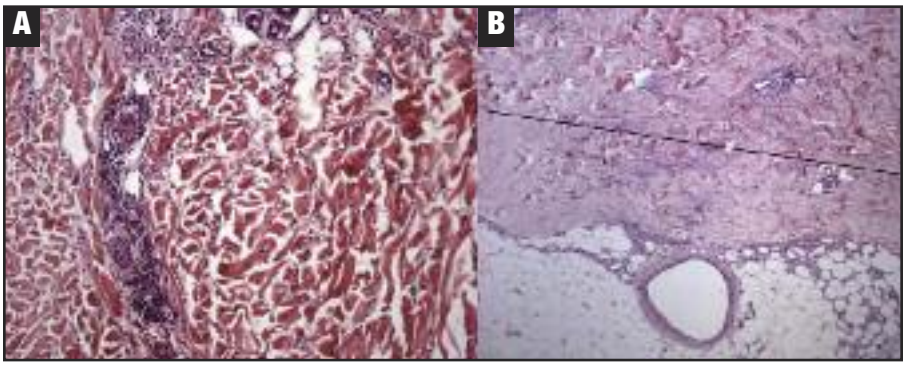

Figure 2. Dermis overlying adipose treated with mixed PC/SDC solution. Collagen bundles are unaffected. (B) Dermis overlying adipose treated with SDC alone, homogenization and sclerosis of collagen. Figure adapted from Duncan D, Rubin JP, Golitz L, et al. Refinement of technique in injection lipolysis based on scientific studies and clinical evaluation. *Clin Plast Surg.* 2009;36(2):195–209. Elsevier. Adapted with permission.

ADVERSE EVENTS

Phase 1 trials of ATX-101 revealed no effect on systemic lipid profiles, CRP, or IL-6.[27] In Phase 3 studies, 90.8 percent of the low-dose treatment group and 95 percent of the high-dose treatment group reported adverse effects, as compared with 50.8 percent of placebo patients. The most commonly reported adverse effects were expected, and included transient injection-site pain, swelling, bruising, induration, and numbness. The median duration of pain was one day, while swelling lasted 9 to 10 days, and numbness and induration remained for 17 to 25 days.[25] The REFINE-1 trial reported similar findings, but further added two additional adverse events, both of which were purportedly self-resolving. Marginal mandibular nerve paresis was seen in 4.3 percent of patients, with a median duration of 31 days, and dysphagia was noted in 1.6 percent of participants, with a median duration of four days. Overall, severity of adverse effects was noted to decrease with each subsequent injection session.[26]

Reports of mixed PC/SDC-containing compounds list adverse events including pain and edema lasting 48 hours, and hematoma formation for up to 10 days. A small percentage of patients reported transient post-injection nausea, dizziness, or lightheadedness.[13,28,29] Occasional reports of skin ulceration at injection sites are noted in the literature as well, one in association with undisclosed systemic lupus erythematosus (SLE), and another after a patient had post-injection contact of the inner thighs while walking.

Two reports of hives after injection of a solution of PC and SDC were noted in patients with undisclosed soy allergy.[28] Another report noted localized skin loss over the posterior thigh after injection by a novice nurse injector, trained only

by oral instruction. This patient reported previous aggressive liposuction in the treatment area, and the area of ulceration was treated with hyperbaric oxygen, resolving with minimal surface irregularity.[30]

Injection technique seems to be important with regard to adverse events; small aliquots of 0.2mL or less yield the best results, and injectors should maintain appropriate needle depth (approximately 9–11mm on most sites and around 6mm in the neck).[30,31] External compression is contraindicated. In conjunction with post-injection edema, compression can cause compromise of the local blood supply and result in necrosis of the overlying dermis and epidermis.[30]

In comparison of studies with mixed PC/SDC solutions versus SDC alone, side effect profiles are comparable. Concentrations of SDC must be increased when coadministered with PC, as the two compounds form micelles in solution, decreasing the free portion of detergent.[9,32] A study by Rotunda et al, published in 2009,[32] showed no difference in side effect incidence or treatment efficacy when comparing mixed PC/SDC solutions to SDC alone. However, a preceding study, published by Salti et al[9] in 2008, found that patients tended to have greater severity of adverse effects and slower resolution with solutions of pure SDC.[9,32]

In 2013, Park et al[33] reported undesirable effects after injection of a compound similar to Lipostabil endovena. Lipobean® (Ami Pharm Inc., Korea), a mixed solution of PC and SDC, was utilized on a young woman who desired fat reduction in the abdomen. The patient had a persistent periumbilical nodule six months post-treatment despite three rounds of intralesional triamcinolone. This nodule was removed via excisional biopsy and assessed histologically. Adipose tissue had been replaced by fibrosis with marked inflammatory infiltration and microabscess formation in the dermis. Septal and lobular panniculitis were noted with thick fibrous septa, fat necrosis, and microcyst formation.[33] Purportedly, long-term granuloma formation and persistent induration are more likely to occur when doses of greater than 0.2mLs are utilized and when SDC concentrations are too high.[34]

A single case report from Germany in 2011 reported drug-induced liver dysfunction and tubulointerstitial nephritis, requiring temporary hemodialysis following subcutaneous use of Lipostabil. The patient recovered without long-term disability.[35]

INDICATIONS

To date, the only FDA-approved indication of subcutaneous SDC injection is moderate-to-severe convexity or fullness associated with submental fat.[14] Registered FDA-approved clinical trials have also assessed the safety and efficacy of ATX-101 in the treatment of lipomas, but no indication has been granted. Further study is required to determine whether solutions of PC/SDC may also be used to treat excess fat in other areas of the body.

CONCLUSION

Injections of solutions containing PC and SDC have been used extensively in South America, and may represent a viable alternative for treatment of small pockets of adipose tissue not amenable to other treatment modalities. ATX-101 is the first FDA-approved solution of SDC for subcutaneous injection, but a potential void exists for products containing PC as well. Head to head studies of PC/SDC mixed solutions against SDC alone have shown decreased duration of adverse effects with the mixed solution, but subsequent reports did not note this difference. Further research is indicated and may lead to more tolerable treatments.[9,25,32]

Injection adipolysis solutions containing SDC appear to have a predictable adverse effect profile, with expected pain, swelling, and numbness over the initial post-injection period, and potential for a small percentage of patients to exhibit post-injection paresis of the marginal mandibular nerve, or dysphagia. All of these side effects resolved spontaneously, although rare reports of persistent granuloma formation and skin ulceration with resultant scarring exist. This risk can be somewhat mitigated by questioning patients about personal history of koebnerizing skin disease, connective tissue disease, prior surgical and nonsurgical treatments to the area, and history of soy allergy with solutions containing soy-derived PC. Ensuring that patients do not compress the injection area after the procedure may reduce the risk of ulceration.[17,28,33]

The active ingredient in these preparations has definitively been shown to be SDC, and the mechanism of action is via adipocyte

cytotoxicity, not by induction of intracellular lipases as was previously thought. However, serial histological studies indicate that SDC may be better tolerated and lead to more cosmetically favorable patterns of fat necrosis and fibrosis when coadministered with PC.[17]

Injection-associated nausea, dizziness, and lightheadedness have also been reported. Some degree of injection-associated fibrosis is desirable and may improve skin laxity after treatment, leading to improved cosmesis, particularly in the submental area.[17,31]

Future injectables derived from mesotherapeutic agents are also currently in development. Drugs that activate intracellular lipases via the effects of beta-adrenergic stimulation of adipocytes are in development, with the resulting temporary loss of adipose volume being termed injection lipolysis. Neothetics Corporation, formerly known as Lithera, has two formulations of salmeterol-based injectables that have completed FDA trials (LIPO-102 and LIPO-202) [Neothetics Corporation Pipeline. http://www.neothetics.com/what_we_do.html]. These may offer a safer alternative for injectable treatment of adipose tissue in the future, with decreased risk of disfiguring side effects, though early experience indicates results are temporary, and tachyphylaxis to beta-adrenergic agents quickly occurs in adipocytes when not used in conjunction with corticosteroids.[2,3,36]

Injectable agents based on mesotherapeutic preparations represent a new category of drugs targeting unwanted adipose tissue. FDA-approved trials of combined PC/SDC solutions and beta-adrenergic agents for injection lipolysis may lead to safer and more consistent results than past trials, which utilized proprietary intravenous formulations, multi-agent injections, and compounded drugs from differing pharmacies and manufacturers. In the meantime, ATX-101 seems to be a safe and effective treatment for submental fat deposits when in the hands of an experienced injector.

REFERENCES

1. Lozinski A, Huq NS. Tumescent liposuction. *Clin Plast Surg.* [Internet]. Elsevier Inc; 2013;40(4):593–613. http://dx.doi.org/10.1016/j.cps.2013.07.006.
2. Friedmann DP. A review of the aesthetic treatment of abdominal subcutaneous adipose tissue. *Dermatol Surg* [Internet]. 2015;41(1):18–34. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00042728-201501000-00003.
3. Jayasinghe S, Guillot T, Bissoon L, Greenway F. Mesotherapy for local fat reduction. *Obes Rev.* 2013;14(10):780–91.
4. Reeds DN, Mohammed BS, Klein S, et al. Metabolic and structural effects of phosphatidylcholine and deoxycholate injections on subcutaneous fat: a randomized, controlled trial. *Aesthet Surg J* [Internet]. 2013;33(3):400–408. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3667691&tool=pmcentrez&rendertype=abstract.
5. Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg.* 2004;30(7):1001–1008.
6. Schröder D, Buttenschön K, Herrmann F, Brede S. Is there a drug treatment approach for prevention and therapy of fat embolism syndrome? *Klin Wochenschr.* 1991:229–233.
7. Janke J, Engeli S, Gorzelniak K, Luft FC, Jordan J. Compounds used for "injection lipolysis" destroy adipocytes and other cells found in adipose tissue. *Obes Facts.* 2009;2(1):36–39.
8. Rotunda AM. Injectable treatments for adipose tissue: Terminology, mechanism, and tissue interaction. *Lasers Surg Med.* 2009;41(10):714–720.
9. Salti G, Ghersetich I, Tantussi F, et al. Phosphatidylcholine and sodium deoxycholate in the treatment of localized fat: a double-blind, randomized study. *Dermatol Surg.* 2008;34(1):60–66.
10. Bobkova VI, Lokshina LI, Korsunskiĭ VN, Tananova G V. Metabolic effect of lipostabil-forte. *Kardiologiia*. 1989;29(10):57–60.
11. Mel'chinskaia EN, Gromnatskiĭ NI, Kirichenko LL. Hypolipidemic effects of alisat and lipostabil in patients with diabetes mellitus. *Ter Arkh.* 2000;72(8):57–58.
12. Young VL. Lipostabil: The effect of phosphatidylcholine on subcutaneous fat. *Aesthetic Surg J.* 2003;23(5):413–417.

13. Rittes PG. Complications of Lipostabil Endovena for treating localized fat deposits. *Aesthetic Surg J.* 2007;27(2):146–149.
14. Kybella [package insert]. Westlake Village, CA: Kythera Biopharmaceuticals, Inc.; 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206333Orig1s000lbl.pdf. Accessed on December 1, 2016.
15. Matarasso A, Pfeifer TM. Mesotherapy and injection lipolysis. *Clin Plast Surg*. 2009;36(2):181–92.
16. Gupta A, Lobocki C, Singh S, et al. Actions and comparative efficacy of phosphatidylcholine formulation and isolated sodium deoxycholate for different cell types. *Aesthetic Plast Surg*. 2009;33(3):346–352.
17. Duncan D, Rubin JP, Golitz L, et al. Refinement of technique in injection lipolysis based on scientific studies and clinical evaluation. *Clin Plast Surg*. 2009;36(2):195–209.
18. Lichtenberg D, Robson RJ, Dennis EA. Solubilization of phospholipids by detergents. Structural and kinetic aspects. *Biochim Biophys Acta.* 1983;737(2):285–304.
19. Lichtenberg D, Ahyayauch H, Goñi FM. The mechanism of detergent solubilization of lipid bilayers. *Biophys J.* 2013;105(2):289–99.
20. Thuangtong R, Bentow JJ, Knopp K, et al. Tissue-selective effects of injected deoxycholate. *Dermatol Surg.* 2010;36(6):899–908.
21. Rittes PG. The use of phosphatidylcholine for correction of lower lid bulging due to prominent fat pads. *Dermatol Surg.* 2001;27(4):391–392.
22. Hasegawa T, Matsukura T, Ikeda S. Mesotherapy for benign symmetric lipomatosis. *Aesthet Plast Surg.* 2010;34(2):153–156.
23. Nanda S. Treatment of lipoma by injection lipolysis. *J Cutan Aesthet Surg.* 2011;4:135–137.
24. Rotunda AM, Ablon G, Kolodney MS. Lipomas treated with subcutaneous deoxycholate injections. *J Am Acad Dermatol.* 2005;53(6):973–978.
25. Rzany B, Griffiths T, Walker P, et al. Reduction of unwanted submental fat with ATX-101 (deoxycholic acid), an adipocytolytic injectable treatment: results from a phase III, randomized, placebo-controlled study. *Br J Dermatol.* 2014;170(2):445–453.
26. Jones DH, Carruthers J, Joseph JH, et al. REFINE-1, a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial with ATX-101, an injectable drug for submental fat reduction. *Dermatol Surg.* 2016;42(1):38–49.
27. Walker P, Lee D. A phase 1 pharmacokinetic study of ATX-101: serum lipids and adipokines following synthetic deoxycholic acid injections. *J Cosmet Dermatol.* 2015;14(1):33–39.
28. Mahmud K, Crutchfield CE. Lipodissolve for body sculpting: Safety, effectiveness, and patient satisfaction. *J Clin Aesthet Dermatol.* 2012;5(10):16–19.
29. Palmer M, Curran J, Bowler P. Clinical experience and safety using phosphatidylcholine injections for the localized reduction of subcutaneous fat: a multicentre, retrospective UK study. *J Cosmet Dermatol.* 2006;5(3):218–226.
30. Duncan DI, Palmer M. Fat reduction using phosphatidylcholine/sodium deoxycholate injections: standard of practice. *Aesthetic Plast Surg.* 2008;32(6):858–872.
31. Rittes PG. The lipodissolve technique: clinical experience. *Clin Plast Surg.* 2009;36(2):215–221.
32. Rotunda AM, Weiss SR, Rivkin LS. Randomized double-blind clinical trial of subcutaneously injected deoxycholate versus a phosphatidylcholine-deoxycholate combination for the reduction of submental fat. *Dermatol Surg.* 2009;35(5):792–803.
33. Park EJ, Kim HS, Kim M, Oh HJ. Histological changes after treatment for localized fat deposits with phosphatidylcholine and sodium deoxycholate. *J Cosmet Dermatol.* 2013;12(3):240–243.
34. Rotunda AM. Commentary: mixed-cell granulomatous panniculitis on the cheek due to injection of solution containing phosphatidylcholine and deoxycholate. *Dermatol Surg.* 2010;36(11):1782–1785.
35. Rey JW, Schreiner O, Barreiros AP, et al. Acute renal failure and liver dysfunction after subcutaneous injection of 3-sn-phosphatidylcholine (Lipostabil®)—case report. *Z Gastroenterol.* 2011;49(3):340–343.
36. Tanner B, Barabas T, Crook D, Link C. A future for injection lipolysis? *Aesthet Surg J.* 2013;33(3):456–457.